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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,128	BRIAND, JACQUES	
	Examiner	Art Unit	
	Mark L. Shibuya, Ph.D.,	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10 and 17-19* is/are pending in the application.

4a) Of the above claim(s) *12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3-8, 10, 12-19 are pending. Claims 12-16 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 3-8, 10, 17-19 are examined.

Priority

2. This application is the national stage entry of PCT/US00/26949, filed 9/29/2000, which claims benefit of Provisional application 60/156,557, filed 9/29/1999.

Withdrawn Claim Objections/Rejections

3. The following objection and rejections to the claims are withdrawn in view of applicant's arguments and amendments to the claims. In particular, applicant's amendments to the claim make clear that the claim terms "substrates" and "product" are limited to the art-recognized namesake participants in enzymatic reactions.

4. Claims 1-11 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth in the previous Office action.

5. Claims 1-4, 6, 7, 9-11, 17, 18, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore et al., (US 2003/0143757).

6. Claims 1-11, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Thompson et al., Proc. Natl. Acad. USA, Vol. 94, pp. 14249-14254 (Dec. 1997).

7. Claims 1-11, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hajduk et al., J. Am. Chem. Soc. 1997, vol. 119, pp. 12257-12261 (IDS filed 2/27/02).

8. Claims 1-4, 6, 7, 9-11, 17 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Fesik et al., (WO 98/48264).

9. Claims 1-4, 6, 7, 9-11, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fesik et al., (WO 97/18469).

10. Claims 1, 2, 4-10, 18, and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Bleicher et al., J. Org. Chem. 1998, 63, 8486-8490.

Claim Objections

11. Claim 1 is objected to because of the following informalities: Claim 1, in the first line, should probably read as "at least one chemical compound that interacts".

Appropriate correction is required. The examiner respectfully requests applicant's assistance in identifying any other such minor informalities that might be present in the amended claims.

Claim Rejections - 35 USC § 112

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 1, 3-8, 10, 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for lack of written description.

This rejection is maintained for the reasons of record, as set forth in the previous Office action. The rejection is copied below for the convenience of the reader. This rejection is necessitated by applicant's amendments to the claims.

The claims are drawn to methods comprising substrates and products "of a target molecule". The specification, for example at p. 8, lines 29-30, contemplate that "[a]n embodiment of the present invention provides a target molecule involved in a catalytic reaction of a substrate into a final product." The specification at, e.g., p. 13, lines 16-19, states that "[t]argets, products, ligands and substrates of the invention may be polypeptides and/or polynucleotides." The specification, at p. 14, lines 17-21, states that "[i]n preferred embodiments each of the wells in a multiwell format is loaded with one or more compounds, an invariant concentration of substrate and/or ligand and/or product, and an invariant concentration of target, most preferably an enzyme, either of protein or a ribozyme." The specification at p. 19, Example 1, Figures 1 and 2, describes "deformylation of For-Met-Ala-Ser-OH by Peptide Deformylase (S.Aureus) when 8-hydroxyquinoline is present in the solution."

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

One of skill in the art cannot envision the detailed sequence or chemical structure of the encompassed substrates or products of any target molecule, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. In so far as the specification contemplates substrates or products as enzyme substrates or enzyme products, the specification does not describe a representative number of species to adequately describe the broad genus of "target molecules". The specification states that target molecules may be polypeptides or polynucleotides, however, the specification does not limit the definition of target molecules; and does not limit the definition of target molecules to enzymes. The specification provides a single example wherein the target molecules is a S. aureus peptide deformylase, and a single substrate that is For-Met-Ala-Ser-OH. The specification as filed does not describe a single enzyme product, including an enzyme product used in the assay, when the target molecule is peptide deformylase. The specification at p. 8, line 33, shows a reaction scheme in which an enzyme product "P", is depicted as not associated with, but separate from an enzyme "E". The specification does not describe what spectrum results when a product and at least one compound are exposed to a target molecule or even to a target molecule that is an enzyme. The specification does not describe a representative number of substrates or products for any target molecule. The specification does not point to where in the art such information exists. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of using it. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Furthermore, all of the claims, except for claim 9, are drawn generally to a first spectrum and a second spectrum, without limitation as to the type of spectrum. The specification, for example at p. 2, lines 1-2, states that "[t]he present invention relates to methods using one-dimensional and multi-dimensional NMR spectroscopy for identifying ligands to target biomolecules." The specification does not describe any other type of spectroscopy or methodology or generating spectra. Thus the specification does not describe a representative number of species of methodology to adequately describe the genus of methods of generating spectra.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The amended claims are drawn to a method of identifying at least one chemical compound that interact with an enzyme comprising the steps of: a) mixing a substrate or product of said enzyme with at least one said chemical compound; b) generating a first NMR spectrum that displays either a chemical shift in the first dimension or a chemical shifts in the other dimension of said substrate or product in step a); c) exposing the mixture of said substrate or product and at least one said chemical compound in step a) to said enzyme for one or more incubation times; d) generating a second NMR

spectrum that displays either a chemical shift in the first dimension or a chemical shifts in the other dimension of substrate or product in step a) that has been exposed to said enzyme in step c) in the presence of at least one chemical compound in step a); e) comparing said first NMR spectrum and second NMR spectrum after one or more said incubation times in step c) to determine at least one difference between said first NMR spectrum and second NMR spectrum, the differences observed along either or both chemical shift dimensions identifying transformation of said substrate or product and classifying the presence of at least one said chemical compounds that interact with said enzyme.

Response to Arguments

Applicant argues that the specification provides adequate written description for methods using enzymes or NMR techniques identifying chemical compounds that interact with a target enzyme.

Applicant's arguments, entered 9/1/2006, have been fully considered but they are not persuasive. As previously stated, in so far as the specification contemplates substrates or products as enzyme substrates or enzyme products, the specification does not describe a representative number of species to adequately describe the broad genus of "target molecules". The specification states that target molecules may be polypeptides or polynucleotides, however, the specification does not limit the definition of target molecules; and does not limit the definition of target molecules to enzymes. The specification provides a single example wherein the target molecules is a S. aureus

peptide deformylase, and a single substrate that is For-Met-Ala-Ser-OH. The specification as filed does not describe a single enzyme product, including an enzyme product used in the assay, when the target molecule is peptide deformylase. The specification at p. 8, line 33, shows a reaction scheme in which an enzyme product "P", is depicted as not associated with, but separate from an enzyme "E". The specification does not describe what spectrum results when a product and at least one compound are exposed to a target molecule or even to a target molecule that is an enzyme. The specification does not describe a representative number of substrates or products for any target molecule. The specification does not point to where in the art such information exists. Therefore, the examiner respectfully submits that one of skill in the art would not envision that the applicant had possession of the full scope of the claimed invention.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 3-8, 10, 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Fesik et al., (WO 98/48264)**, (of record), and in view of **Peters et al.**, Biochemistry 1992, Vol. 31, pp. 10024-10030.

The amended claims are drawn to a method of identifying at least one chemical compound that interact with an enzyme comprising the steps of: a) mixing a substrate or product of said enzyme with at least one said chemical compound; b) generating a first NMR spectrum that displays either a chemical shift in the first dimension or a chemical shifts in the other dimension of said substrate or product in step a); c) exposing the mixture of said substrate or product and at least one said chemical compound in step a) to said enzyme for one or more incubation times; d) generating a second NMR spectrum that displays either a chemical shift in the first dimension or a chemical shifts in the other dimension of substrate or product in step a) that has been exposed to said enzyme in step c) in the presence of at least one chemical compound in step a); e) comparing said first NMR spectrum and second NMR spectrum after one or more said incubation times in step c) to determine at least one difference between said first NMR spectrum and second NMR spectrum, the differences observed along either or both

chemical shift dimensions identifying transformation of said substrate or product and classifying the presence of at least one said chemical compounds that interact with said enzyme.

Fesik et al., (WO 98/48264), throughout the publication, and at p. 1, lines 2-4, p. 2, line 23-p. 3, line 12, p. 4, line 18-p.4, line 33, p. 7, line 32-p. 8, line 37, p. 10, lines 10-19, p. 10, line 35-p. 11, line 2, teaches: a) generating a first T2- or diffusion-filtered proton spectrum of one or a mixture of chemical compounds; b) exposing one or a mixture of chemical compounds to the target molecule; c) generating a second T2- or diffusion filtered proton spectrum of one or a mixture of chemical compounds that has been exposed to the target molecule in step (b); and d) comparing said first and second T2- or diffusion-filtered proton spectra to determine differences between said first and said second spectra, the differences identifying the presence of one or more compounds that are ligands which have bound to the target molecule. Additional steps comprise the steps of e) generating a T2- or diffusion-filtered proton spectrum of each compound in the mixture f) exposing each compound in the mixture individually to the target molecule, g) generating a T2- or diffusion-filtered proton spectrum of each compound in the mixture after exposure to the target molecule h) comparing each spectrum generated in step g) to the first spectrum generated from the target molecule alone to determine differences in any of those compared spectra, the differences identifying the presence of a compound that is a ligand which has bound to the target molecule; wherein the target is a polypeptide, which is a biomolecule. Fesik et al. teaches use of a sample changer with a total of 60 samples that can be run unattended

and computer programs to facilitate transfer and automatic processing of multiple one-dimensional NMR data.

Fesik et al., (WO 98/48264), at p. 1, lines 16-20, discloses that the prior art teaches assaying enzyme reactions. Fesik et al., (WO 98/48264) at p. 2, lines 33-37, teaches that screening more than compound or a mixture of compounds prior to exposing the mixture to the target molecule, is desirable because an active compound can be identified immediately if the spectrum of the active compound in the absence of the target molecule is known.

Fesik et al., (WO 98/48264), does not disclose an NMR method comprising mixing a substrate or product of said enzyme with at least one said chemical compounds; and then exposing the mixture of said substrate or product and at least one said chemical compound, to said enzyme. Fesik et al., (WO 98/48264), does not disclose an NMR method comprising first and second NMR spectrum displaying chemical shifts in a first and other dimensions selected from the group consisting of 1H, 3H, 11B, 13C, 15N, 19F 29S and 31P, (as in claims 5 and 8).

Peters et al., throughout the publication, and describe a method of identifying at least one chemical compounds that interact with an enzyme comprising the steps of: at e.g., p 10027, para 5 and Table I, fn.1, p. 10025, para 3, 4, 13, teach determining NMR data for samples of the enzyme phospholipase A2 (PLA) and fully deuterated *n*-dodecylphosphocholine (DPC) in micellar form, reading on a substrate of PLA, and the inhibitor (R)-2-(dodecanolylamino)hexanol-1-phosphoglycol. Peters et al., at e.g., p. 10028, para 7-10, p. 10028, para 15, p. 10029, para 2-3, teach that upon binding of the

enzyme, substrate and inhibitor, thereby forming a ternary complex, there are pronounced changes in the chemical shift of the enzyme's backbone, which are probably due to conformational changes. Peters et al., at pp. 10025, second column-10027, first column, and Fig. 2, disclose an NMR method comprising first and second NMR spectrum displaying 1H and 15N chemical shifts in a first and second dimensions.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used NMR methods of identifying compounds that interact with enzymes, wherein an enzyme substrate or product is mixed with at least one said chemical compounds; and wherein the mixture of said substrate or product and at least one said chemical compound, is exposed, subsequently, to said enzyme.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used NMR methods comprising first and second NMR spectrum displaying chemical shifts in a first and other dimension selected from the group consisting of 1H, 3H, 11B, 13C, 15N, 19F 29S and 31P, (as in claims 5 and 8).

One of ordinary skill in the art would have been motivated to make and use NMR methods wherein an enzyme substrate or product is mixed with at least one said chemical compounds because Peters et al., at e.g., p. 10028, para 7-10, p. 10028, para 15, p. 10029, para 2-3, teach that it is desirable to measure binding of the enzyme, substrate and inhibitor, in a ternary complex, in order to achieve and detect pronounced changes in the chemical shift of the enzyme's backbone, which are probably due to

conformational changes. One of ordinary skill in the art would have been motivated to make and use NMR methods comprising mixing a substrate or product of said enzyme with at least one said chemical compounds; and then exposing the mixture of said substrate or product and at least one said chemical compound, to said enzyme, because Fesik et al., (WO 98/48264) at p. 2, lines 33-37, teaches that screening more than compound or a mixture of compounds prior to exposing the mixture to the target molecule, is desirable because an active compound can be identified immediately if the spectrum of the active compound in the absence of the target molecule is known.

One of ordinary skill in the art would have been motivated to make and use NMR methods It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used NMR methods comprising first and second NMR spectrum displaying chemical shifts in a first and other dimension selected from the group consisting of 1H, 3H, 11B, 13C, 15N, 19F 29S and 31P, (as in claims 5 and 8) because Peters et al., at p. 10025, teach the use of high-resolution NMR spectroscopy to obtain detailed information about the structure of the ternary complex of protein bound to a micelle, reading on a substrate, and containing a single inhibitor molecule in its active site.

One of ordinary skill in the art would have had a reasonable expectation of success in using such methods because Peters and Fesik teach the NMR identification of compounds that interact with proteins, including enzymes.

Conclusion

16. Claims 1, 3-8, 10, 17-19 stand finally rejected. Claim 1 is objected to.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya, Ph.D., whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. James Schultz can be reached on (571) 272-0763. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1639